AMBULATORY FLUOROQUINOLONE USE IN THE UNITED STATES, 2014 to 2019

by

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ABSTRACT

Importance. Fluoroquinolones have been subject to increasing safety concerns and regulatory advisories. In the face of emerging risks, some evidence suggest they remain widely prescribed in ambulatory settings, and the impact of regulatory risk communications remains unclear.

Objectives. i) To quantify and characterize ambulatory fluoroquinolone utilization in the United States between January 2014 and December 2019, and ii) to evaluate the effect of 2016 U.S. Food and Drug Administration (FDA) advisories on fluoroquinolone use.

Design, participants and outcomes. We used IQVIA's National Disease and Therapeutic Index (NDTI) to quantify quarterly and annual outpatient visits where a fluoroquinolone was used among individuals age $\geq$ 20 years. We used descriptive statistics to report the utilization trends from 2014 to 2019, stratified by fluoroquinolone type, diagnoses and prescriber characteristics; and segmented-regression analysis to quantify the impact of 2016 FDA risk communications on fluoroquinolone use.

Results. Between 2014 to 2019, fluoroquinolone use decreased by 27.8%. Ciprofloxacin accounted for highest number of treatment visits (58.39 %), followed by levofloxacin (34.14 %). Over the six-year period, utilization decreased among non-surgeons by 37.3%; whereas, use increased by 25.6% among surgeons. The magnitude of fluoroquinolone use varied remarkably by clinical indication and provider age. For example, use declined by 45.9% for respiratory conditions vs 28.5% for urogenital conditions vs 20.4% for gastrointestinal conditions. Fluoroquinolone use declined by 73.9% among providers $\leq$ 44 years-old compared to a decline that ranged from 1- 40% among those $\geq$ 45 years-old. Prior to the 2016 regulatory advisories, there were ~ 4.8 million fluoroquinolone treatment visits per quarter. In the post-advisory period, there was a statistically significant level drop by 641,035 visits (p-value = 0.000, 95% C= -937368, -344702) and a statistically significant difference in pre and post utilization trends by ~45k visits (p-value = 0.036 -85956, -3122.345)

Conclusions and Relevance. Large reductions in ambulatory fluoroquinolone use in the United States have coincided with increasing evidence and FDA risk communications regarding of their potential risks. Despite this, changes in fluoroquinolone use have varied based on patient and provider characteristics, suggesting heterogeneous effects of emerging risks on clinical practice.

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INTRODUCTION

The first fluoroquinolone, Norfloxacin, was approved by the U.S. Food and Drug Administration (FDA) in 1986 for treating genitourinary infections. Since then, six additional fluoroquinolone products (ciprofloxacin, ofloxacin, gemifloxacin, levofloxacin, moxifloxacin and delafloxacin) have been approved by the FDA.[1] These products are widely prescribed and are ranked as the fourth most commonly prescribed antibiotic class in the United States, [2] in part because of their wide spectrum of activity, excellent bioavailability, extensive penetration in tissue and successful microbiological outcomes.[3]

Despite their clinical value, fluoroquinolones are associated with a host of potential adverse effects. Some of these, such as diarrhea, nausea, and headaches, have been well described in the drug label since their earliest FDA approval. However, other more severe safety concerns have been increasingly well characterized over the past few decades. For example, fluoroquinolone-induced achilles tendinopathy, first reported in New Zealand in 1983, has since been well described in numerous observational studies.[4,5] Meta-analysis of studies on fluoroquinolone associated tendinopathies suggests that fluoroquinolone users have a two and a half times higher risk of achilles tendon rupture, fourfold higher risk of achilles tendinitis, and two-fold higher risk of any tendon disorder, as compared non-users, a risk that is especially elevated among elderly individuals. [6] Similarly, fluoroquinolone users are twice likely to suffer from peripheral neuropathy than non-users.[7] The risk is dose-dependent and increases by 3% with every additional day of exposure.[8] Fluoroquinolones are also known to induce mental disturbances such as psychoses, disorientation, agitation, nervousness, impaired memory and delirium. [9,10] Case reports and observational studies also suggest a dose - duration dependent risk of aortic aneurysm, dissection, tears and ruptures among fluoroquinolone users. [11 -14.]

Increasing discovery of side effects has led to multiple FDA safety alerts and advisories for these products (Appendix 1). In July 2008, FDA released a boxed warning to address the specific risk of tendinitis and tendon rupture among fluoroquinolone users, [15] followed by another warning in August 2013 addressing the risk of irreversible peripheral neuropathy[16]. In May 2016, FDA issued a safety alert cautioning the prescribers about potentially disabling side-effects of fluoroquinolones affecting two or more organ systems and recommended to avoid its use in acute uncomplicated infections. Consequently, in July 2016, FDA approved a class-wide label change for addressing risk of central nervous system side-effects and peripheral neuropathy and limiting use of fluoroquinolones in acute uncomplicated infections. [17] More recently still, in 2018, FDA noted fluoroquinolones' associated risk of severe hypoglycemia, mental side-effects such as disorientation and impaired memory and risk of aortic aneurysm, dissection, tear and rupture potentially causing fatal bleeding.[18]

In face of emerging safety concerns over the past decade, fluoroquinolone utilization has been consistently high.[19] For example, fluoroquinolone prescribing in the United States rose 3-fold from 1995 to 2002 and was the most commonly prescribed antibiotic across all types of care - settings in 2009. [20,21] In 2016, fluoroquinolone antibiotics were the 4th most commonly prescribed class of medicine in outpatient setting of United States. [2]

To our knowledge, fluoroquinolone use in outpatient setting has not been well characterized. In addition, it is unclear whether fluoroquinolone use differs by physician and patient characteristics. Moreover, we do not know the impact of FDA advisories on fluoroquinolone use in outpatient care settings of United States.

Thus, through this study, we sought to characterize the impact of FDA advisories on changes in outpatient fluoroquinolone use and identify characteristics that may inform such change. We hypothesized a decline in fluoroquinolone use over time. Further, we hypothesized that FDA risk

communications may have contributed to such declines by raising awareness among prescribers and patients regarding potential serious adverse effects associated with fluoroquinolone use.

METHOD

Data Source

We used IQVIA's National Disease and Therapeutic Index (NDTI) to obtain annual and quarterly data on fluoroquinolone use from January 2014 through December 2019. NDTI sample is an office-based panel of physicians providing care in both community and academic settings in the continental United States and has been used previously to examine drug utilization.[22-24] The universe of NDTI physicians is obtained from American Medical Association Masterfile and American Osteopathic Association. Approximately 4000 participating physicians report on all patient contacts occurring during two consecutive workdays in each calendar quarter using a web-based form for each patient-encounter. The physicians report patient's demographic details, diagnoses and treatments for every visit. Each therapy record is linked to a 6-digit taxonomy code similar to the World Health Organization's International Classification of Disease, ninth revision (ICD-9). Using sample weights, nationally representative estimates are obtained for ~534,000 physicians all over the US.

Products examined

We used FDA.gov to identify the approved fluoroquinolone products marketed in the United States between 2014 to 2019.[1] We excluded topical fluoroquinolone products such as optic and otic solutions from our analysis since safety concerns regarding fluoroquinolones have been limited to oral formulations. We included all products licensed for marketing in the United States during the study period, including ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, delafloxacin and gemifloxacin.

Statistical Analysis

Our primary unit of analysis was treatment visits, which is defined as an ambulatory visit where an individual was diagnosed with a condition and treated with a pharmacologic product. Thus, every fluoroquinolone treatment visit account for an ambulatory visit where fluoroquinolone was either initiated or continued.

Descriptive analysis

Using annual and quarterly (Q) estimates from January 2014 to December 2019, we used descriptive statistics to analyze the trends of fluoroquinolone utilization. We limited our analysis to adults aged 20 years and older and stratified the utilization by key patient (age, sex, diagnosis) and prescriber (specialty, age) characteristics. We used mutually exclusive diagnosis categories based on major organ systems such as urogenital system, respiratory system, gastrointestinal system, skin/musculoskeletal system, blood/lymphatic system/cancer, and otolaryngology. We grouped the providers into 2 broad categories, non-surgeons and surgeons (Appendix 2). Non-surgeons consisted of primary care physicians, internal medicine doctors and non-surgeons. For ease of reporting the results, we grouped the fluoroquinolone products in 3 broad categories, ciprofloxacin, levofloxacin and 'other fluoroquinolones.' The category 'other fluoroquinolones' consists of moxifloxacin, ofloxacin, delafloxacin and gemifloxacin. We also examined the fraction of overall treatment visits for urogenital, respiratory, and gastrointestinal conditions that were accounted for by fluoroquinolone product and stratified these findings by prescriber specialty. For all yearly estimates, we derived 95% confidence intervals using information about standard errors accompanying the survey sampling methodology (Appendix 3).

Impact of FDA advisories on fluoroquinolone use

Using an interrupted time-series analysis we examined the effect of 2016 FDA advisories on trends in fluoroquinolone use from January 2014 to December 2019. Prior to this analysis we , identified the ideal inflection points in our segmented analysis by i) visually inspecting the quarterly trends of fluoroquinolone use while superimposing the FDA advisories of interest on order to examine quarterly trends in fluoroquinolone use; and ii) using Joinpoint regression, a permutation method developed by the National Cancer Institute, to test for possible inflection points in time-series data without defining interventions a priori.[25,26] Visual inspection of the data and Joinpoint regression suggested significant inflection points at the second and third quarter of 2016, respectively. These inflection points closely coincided with the FDA's May 2016 and July 2016 advisories. (Appendix 4)

Considering the lag time and overlapping effects of May 2016 and July 2016 FDA advisories, we examined their combined effect by collapsing the 2016 Q2 and 2016 Q3 into one time point labelled as 'advisory period'. Thus, our study period consists of i) pre-advisory period of 9 quarters, from 2014 Q1 to 2016 Q1; ii) advisory period of 2 quarters, 2016 Q2 and 2016 Q3; iii) post-advisory period of 13 quarters, from 2016 Q4 to 2019 Q4.

We modeled the data using a linear trend model in which outcome variable was defined as average number of treatment visits per quarter. The regression included a linear trend, a dummy variable for the post-advisory period, and an interaction term. Thus, we could directly estimate the immediate change (level) of fluoroquinolone use after the advisories were issued and compare the pre-advisory and post-advisory trends (slope) in fluoroquinolone use. The model's goodness-of-fit was examined by the value of R-square statistic (0.89). This was further supported by plots of residual versus fitted values, and histogram of residuals suggesting random variance in the data. We examined for autocorrelation and seasonal trends using

correlograms derived by Bartlett's formula and lagged correlation, respectively. We did not identify statistically significant autocorrelation or seasonal trends in the data.

The results of segmented regression analysis were reported as i) average number of treatment visits per quarter in the pre-advisory period (pre-alert utilization trend); ii) immediate impact of advisories on utilization (level change); iii) average number of treatment visits per quarter in post-advisory period (post-alert utilization trend); iv) the difference in pre and post utilization trends. The statistical significance was determined by 95% confidence intervals and p-value.

Descriptive analysis was performed using Microsoft Excel (version 16.34) and segmented regression analysis was performed using STATA software (version 15). This study was exempt from Johns Hopkins Institutional Board Review as it did not constitute human subjects research.

RESULTS

Overall utilization of fluoroquinolone antibiotics, 2014 to 2019

Between January 2014 and December 2019, fluoroquinolone use declined by nearly one third (27.8%), from approximately 19.1 million treatment visits in 2014 to 13.8 million treatment visits in 2019. Ciprofloxacin and Levofloxacin were the top-selling fluoroquinolone products accounting for more than 90% of the market share during this period. The remaining 10% treatment visits were accounted for other types of fluoroquinolones (moxifloxacin, ofloxacin, delafloxacin, and gemifloxacin). By the end of 2019, there was a 40.9% decline in Levofloxacin use, 26.9% decline in Ciprofloxacin use, and 59.3% increase in use of other types of fluoroquinolones (Table 1, Figure1). The quarterly trends of fluoroquinolone utilization showed a 30.7% decline over 6 years, with largest decline (14.19%) observed in 2016 Q2. (Figure 2)

Trends in fluoroquinolone use by prescriber specialty, 2014 to 2019

Over the period examined, approximately 13.3 million (81%) treatment visits/year were accounted for by non-surgeons whereas approximately 3 million (19%) treatment visits/year were accounted for by surgeons. By the end of 2019, fluoroquinolone use among non-surgeons declined by 37.3%, from 16.2 million treatment visits in 2014 to 10.1 million treatment visits in 2019. Among surgeons, fluoroquinolone use increased by 25.6%, from 2.8 million treatment visits in 2014 to 3.6 million treatment visits in 2019. (Table 1)

Trends in fluoroquinolone use by diagnosis, 2014 to 2019

The highest number of treatment visits were accounted for by urogenital conditions, with an average of 6.9 million (43%) treatment visits/year. The second highest use was accounted for by respiratory conditions, with an average of 4.9 million (30.2%) treatment visits/year. Gastrointestinal conditions accounted for approximately 1.5 million (9.6%) treatment visits/year.

Conditions affecting the skin or musculoskeletal system, blood, lymphatic systems, and cancers accounted for fewer than 10% of all fluoroquinolone treatment visits per year. By the end of 2019, fluoroquinolone use for respiratory conditions declined by 46%, from 6.3 million treatment visits in 2014 to 3.4 million treatment visits in 2019. Similarly, use declined by 28.5% for urogenital conditions and 20.3% for gastrointestinal conditions. (Table1, Figure 3)

Proportion use of fluoroquinolones over all treatment visits, 2014 to 2019

Among non-surgeons, although the overall number of treatment visits for urogenital conditions increased by 6.9% (3 million in 2014 to 3.2 million in 2019), the treatment visits accounted for by fluoroquinolone products declined by 83.8% (6.7 million in 2014 to 1.1 million in 2019); whereas, among surgeons, the overall treatment visits for urogenital conditions decreased by 6.9% and the fraction accounted for by fluoroquinolone products increased by 12.5 %, from 1.1 million in 2014 to 1.2 million in 2019.

From 2014 to 2019 the overall number of treatment visits for respiratory conditions among both specialties of care showed moderate decline by ~7%; however, the fraction of treatment visits accounted for by fluoroquinolones showed large declines by 45.7% among non-surgeons and 59.5% among surgeons.

Over the study period, fraction of treatment visits for gastrointestinal conditions accounted for by fluoroquinolone products decreased by 26% among non-surgeons and increased by 2.8% among surgeons. (Table 2 and Table 3)

Trends in fluoroquinolone use by prescriber age, 2014 to 2019

Between 2014 to 2019, on an average 134,000 (8%) treatment visits/year were accounted for by physicians ≤44 years; whereas, 15 million (92%) treatment visits/year were accounted for by physicians ≥ 45 years old. Fluoroquinolone use was highest among physicians 55-64 years,

accounting for approximately 4.3 million (40%) of treatment visits/year. Over the period examined, larger declines in use were observed among younger physicians. For example, from 2014 to 2019 the number of fluoroquinolone treatment visits among physicians ≤ 44 years declined by 74% (from 2.1 million in 2014 to 549,000 in 2019) as compared to 40.3% (from 4.9 million in 2014 to 2.9 million in 2019) decline among those 45-54 years old, 22.3% (from 7.5 million to 5.8 million) decline among those 55-64 years old and 1% (from 4.46 million to 4.42 million) decline among those >65 years old. (Table 1)

Impact of 2016 FDA advisories on fluoroquinolone use

In the pre-advisory period (2014 Q1 – 2016 Q1), fluoroquinolone use was approximately 4.8 million treatment visits/quarter with a statistically non-significant decline of 9274 treatment visits/ quarter (p-value = 0.51, 95% CI = -38184, 19637). Immediately after the 2016 FDA advisories (2016 Q2 & 2016 Q3), there was a statistically significant decline in fluoroquinolone use by 641,035 treatment visits (p-value = 0.000, -937368, -344702). In the post-advisory period (2016 Q4 - 2019 Q4) fluoroquinolone use was approximately 4.1 million treatment visits/quarter. The pre-advisory and post-advisory trends in fluoroquinolone use showed a statistically significant difference of 44,539 treatment visits (p-value = 0.036, -85956, -3122). (Table 4)

DISCUSSION

While declines in fluoroquinolone use preceded the 2016 FDA regulatory advisories, these risk communications were associated with further statistically significant decline in use. Over the study period, fluoroquinolone use declined by more than 25 %; characterized by highest decline for respiratory conditions. Changes in use varied remarkably by provider's age, with younger physicians much more likely to decrease fluoroquinolone use than their older counterparts. These findings are important because they suggest the underlying differences among prescribers which affect the trends in utilization of a drug that is associated with multiple safety concerns.

Our study reports a sizeable decline (~28%) in fluoroquinolone use and statistically significant association of 2016 FDA advisories with further declines in fluoroquinolone use. These findings are supported by another study evaluating the impact of July 2016 FDA alert on in-patient utilization of fluoroquinolones across 29 southeastern hospitals of the United States, from 2013 to 2017. The authors reported ~25 % decline in fluoroquinolone use in the pre-advisory period from January 2013 to July 2016, a statistically significant decline by 7.6% immediately following the alert in August 2016, followed by statistically non-significant decline by 0.9% per month in the post-alert phase from August 2016 to December 2017. [27] Other similar studies have reported small and statistically non-significant decelerations in fluoroquinolone use after FDA's July 2016 alert.[28,29] The immediate and long-term declines observed in this study can be explained by the overlapping effects of adjacent FDA alerts, considering the lead and lag time for each alert to take into effect. Moreover, in 2018, FDA issued two other safety alerts for fluoroquinolone antibiotics highlighting the serious risks such as hypoglycemia, mental disturbances, and aortic aneurysm tears or rupture. These alerts could probably have an additional effect on the declining utilization trends. Furthermore, the declines in fluoroquinolone use could be attributed to factors such as the provider and patient response to emerging safety

information, antibiotic stewardship programs (ASPs) and educational activities aimed at clinicians and patients. [30-32] In the recent past, ASPs have been a source of focused effort to improve the patient-outcomes and optimize antibiotic use. ASP associated reduction in unnecessary prescribing and improved selection of antibiotics has been well-discussed in previous studies.[32] For example, Lin et al reported that a multi-modal ASP implemented in outpatient clinic, emergency care and urgent emergency care center of a hospital in Texas led to 34% decline in fluoroquinolones use and the proportion of inappropriate use of fluoroquinolones decreased from 53% in October 2016 to 34% in October 2018 [30]. Other factors such as secular trends in infection rates, changes in clinical guidelines, and new antibiotic products being brought to market may also play a role in the changing utilization trends.

In this study, the largest proportion for fluoroquinolone treatment visits were accounted for by urogenital conditions. This finding is strongly supported by a study reported by Kabbani and colleagues, who examined the outpatient fluoroquinolone use in the United States from 2013 to 2014. The authors reported that, fluoroquinolone use was highest for urogenital conditions. Furthermore, ~40% of fluoroquinolone use for urogenital conditions was for uncomplicated urinary tract infections suggesting a high proportion of use contradictory to FDA recommendations. Therefore, the high utilization of fluoroquinolones for urogenital conditions in our study could potentially reflect the inappropriate use of fluoroquinolones. However, it is difficult to determine the rationality of fluoroquinolone use as it is beyond the scope of this study.[33] Interestingly, the large decline in fluoroquinolone use for respiratory conditions that we observed may be attributable to FDA advisories. The May 2016 and July 2016 alerts directly recommend avoiding fluoroquinolone use for acute bacterial sinusitis and bronchitis.[17] Moreover, ASPs are reported to have significant effect on reducing fluoroquinolone use for respiratory conditions. For example, antibiotic stewardship program conducted in a hospital in Texas significantly reduced the fluoroquinolone use by 58% for cystitis and 33% for bronchitis.[34]

Approximately three-fifths of fluoroquinolone use was accounted for by non-surgeons such as primary care physicians, internal medicine doctors and medicine specialties. This finding can be related to the high number of infections treated by primary care doctors or medicine specialists in outpatient settings. This finding can be supported by the 2017 CDC report on outpatient antibiotic use that suggests 1.5 to 3 times higher prescribing of antibiotics by medicine doctors as compared to surgeons.[35] Moreover, antibiotic-decision-making may be perceived as a non-surgical intervention that is often delegated to internal medicine doctors or infection specialists, thus, increasing the probability of non-surgeons to prescribe antibiotics in surgery patients.[36]

By the end of 2019, fluoroquinolone use declined among non-surgeons by 37%; whereas, it increased by 26% among surgeons. This finding could be explained by the underlying differences in clinical practice and effects of evidence on prescribing behaviors. For example, summary of Canadian Medical Associations' Physician Resource Questionnaire suggests that surgical specialists are less likely (32%) to refer online clinical practice guidelines as compared to medicine practitioners (~40%).[37] This could possibly lead to differential dissemination of regulatory advisories and clinical updates among prescriber specialties.

Previous studies strongly support the relationship between physician's age, years of practice and declining quality of clinical care.[38-39] For example, a systematic review determining the relationship between clinical experience and quality of health care reported that, 52% of reviewed studies show declining performance and lower quality of care with increasing years in physician's practice. Physicians less than 40 years old are more likely have better knowledge about value of therapies and clinical updates; whereas, older physicians have less factual knowledge and seem less likely to be receptive to evidence-based practice guidelines.[40] Personal digital assistants which provide easy access to internet and clinical updates are used 1.5 to 2 times higher among younger physicians than older counterparts and physicians using internet have higher impact of literature evidence on their clinical practice.[39-40] Another study

reports that, more than 50% of younger physicians as compared to less than 25% of older physicians refer to online clinical practice guidelines.[37] These findings corroborate and explain the dissimilarities in trends in fluoroquinolone use by prescriber characteristics observed in our study.

STRENGTHS AND LIMITATIONS

We have exclusively examined outpatient fluoroquinolone utilization for a period of 6 years. To our knowledge, no previous study has characterized fluoroquinolone use by patient and prescriber characteristics. Moreover, this study statistically examines the association of two adjacent FDA advisories issued in 2016 on the changing trends in fluoroquinolone use.

Although our study has many strengths, it has several limitations. For example, the NDTI dataset is a survey weighted data with inherent sampling errors. Also, this data does not include approximately 100,000 physicians from specialties such as critical care medicine, preventive medicine and residency programs. Therefore, fluoroquinolones utilization among these specialties is not known. The FDA alerts are in adjacent quarters and therefore the lag in time-to-effect makes it difficult to know the impact of each alert individually. The impact of other factors such as secular trends in infection rates, changes in clinical guidelines, and on-going antibiotic stewardships programs on utilization of fluoroquinolones is not known. Also, data describing use of other antibiotic classes was not available. Therefore, we could not compare the utilization trends of fluoroquinolone antibiotics with other antibiotics which further limited our scope to assess if the observed decline in fluoroquinolone use was associated with an increased use of other antibiotics.

CONCLUSION

In conclusion, fluoroquinolone use among adults in ambulatory care settings has declined remarkably over 6 years. The FDA advisories released in May 2016 and July 2016 had statistically significant association with decline in fluoroquinolone use. However, despite the decrease, the volume of prescribing continues to be high, raising concerns regarding the potential for continued overuse of these products in settings where they may have an unfavorable risk/benefit balance. The dissimilarities in fluoroquinolone utilization by prescriber characteristics suggests underlying differences in attitudes, knowledge and prescribing behavior. Identifying and targeting specific segments of prescribers may further help to reduce fluoroquinolone use.

Table 1: Annual fluoroquinolone use from January 2014 to December 2019.

	2014 (95% CI)	2015 (95% CI)	2016 (95% CI)	2017 (95% CI)	2018 (95% CI)	2019 (95% CI)	% change (2014-2019)
Grand total	19123 (17116, 21131)	18868 (16687, 20849)	16546 (14809, 18283)	15219 (13621, 16817)	14827 (13270, 16384)	13799 (12350, 15248)	-27.8
Product							
Ciprofloxacin	11216 (9714, 12717)	11167 (9671, 12662)	9570 (8288, 10851)	8771 (7553, 9989)	8557 (7368, 9745)	8191 (7006, 9376)	-26.9
Levofloxacin	6968 (5911, 8025)	6772 (5744, 7799)	5828 (4895, 6761)	5139 (4262, 6016)	4999 (4146, 5852)	4113 (4872, 3354)	-40.9
Others [a]	938 (646, 1230)	929 (640, 1217)	1147 (803, 1491)	1309 (917, 1701)	1270 (889, 1651)	1495 (1047, 1943)	59.3
Diagnoses							
Urogenital	8137 (6960, 9314)	7635 (6530, 8740)	7306 (6198, 8414)	6364 (5345, 7383)	6458 (5478, 7438)	5814 (4932, 6696)	-28.5
Respiratory	6279 (5274, 7284)	6372 (5654, 7810)	4927 (4086, 5768)	4347 (3545, 5149)	4272 (3484, 5060)	3398 (2705, 4091)	-45.9
Gastrointestinal	1686 (1289, 2081)	1751 (1339, 2163)	1388 (972, 1804)	1625 (1243, 2007)	1529 (1169, 1889)	1342 (940, 1744)	-20.4
Skin & Musculoskeletal	892 (614, 1169)	881 (607, 1155)	512 (316, 708)	598 (378, 818)	582 (373, 791)	524 (324, 724)	-51.4
Blood/ Lymph/ Cancer	389 (229, 549)	384 (225, 543)	490 (313, 677)	322 (175, 469)	345 (143, 488)	361 (212, 510)	-7.3
Otolaryngology	384 (226, 542)	340 (200, 480)	300 (163, 437)	365 (214, 516)	283 (154, 412)	660 (436, 884)	72.1
Miscellaneous	1293 (905, 1681)	340 (200, 480)	1559 (1192, 1926)	1594 (1219, 1969)	1281 (897, 1665)	1671 (1278, 2064)	29.2

Prescriber specialty							
Medicine	16,166 (14469, 17863)	15832 (14170, 17494)	13462 (11659, 15265)	12222 (10585, 13859)	11,999 (10392, 13606)	10134 (8777, 11491)	-37.3
Surgery	2894 (2304, 3484)	3000 (2388, 3612)	3021 (2405, 3657)	2994 (3605, 2383)	2762 (2199, 3325)	3637 (2969, 4308)	25.6
Prescriber age							
≤44	2107 (1611, 2602)	1613 (1234, 1992)	1628 (1245, 2011)	1350 (1033, 1668)	780 (527, 1033)	548 (352, 744)	-73.9
45-54 years	4966 (4119, 5813)	4873 (4041, 5704)	4330 (3531, 5129)	3495 (2782, 4208)	3230 (2571, 3889)	2963 (2359, 3567)	-40.3
55-64 years	7519 (6431, 8607)	7842 (6707, 8977)	6331 (5317, 7344)	6147 (5163, 7131)	6665 (5654, 7676)	5839 (4907, 6774)	-22.3
≥65 years	4468 (3706, 5230)	4503 (3735, 5271)	4193 (3419, 4967)	4223 (3444, 5002)	4075 (3323, 4827)	4421 (3667, 5175)	-1.05

Use is measured in thousands. Source data is obtained from IQVIA National Disease and Therapeutic Index.

[a] Includes: Ofloxacin, Moxifloxacin, Gemifloxacin, Delafloxacin;

Table 2: Proportion of fluoroquinolone treatment visits over all treatment visits among primary care physicians and non-surgeons.

	2014 (95% CI)	2015 (95% CI)	2016 (95% CI)	2017 (95% CI)	2018 (95% CI)	2019 (95% CI)	% change (2014-2019)
Urogenital conditions							
All treatment visits	30423 (27652, 33195)	27943 (25397, 30489)	28735 (26117, 31353)	30109 (27366, 32852)	32153 (29224, 35082)	32535 (29571, 35499)	6.9
FQ treatment visits	6667 (5656, 7678)	6410 (5438, 7383)	5992 (5033, 6951)	5169 (4287, 6051)	5138 (4261, 6014)	1078 (755, 1401)	-83.8
Proportion use (%)	21.9	22.9	20.8	17.1	15.9	3.3	-84.9
Respiratory conditions							
All treatment visits	69604 (64892, 74316)	66324 (61834, 70814)	57539 (53425, 61653)	62057 (57856, 66258)	65492 (61058, 69926)	64994 (60594, 69394)	-6.6
FQ treatment visits	5922 (4974, 6870)	6025 (5060, 6970)	4586 (3804, 5368)	3910 (3189, 4631)	3999 (3261, 4737)	3213 (2558, 3868)	-45.7
Proportion use (%)	8.5	9.1	7.9	6.3	6.1	4.9	-42.3
Gastrointestinal conditions							
All treatment visits	39825 (36544, 43107)	37588 (34491, 40685)	36927 (33884, 39970)	38627 (35444, 41810)	39580 (36319, 42841)	39874 (36588,43 160)	0.12
FQ treatment visits	1413 (1081, 1745)	1459 (1116, 1802)	1122 (786, 1458)	1350 (945, 1755)	1297 (908, 1686)	1060 (742, 1378)	-24.9
Proportion use (%)	3.5	3.8	3.0	3.5	3.3	2.6	-25.7

FQ = Fluoroquinolone antibiotics
All counts are in thousands.
Proportion use = FQ treatment visits/All treatment visits *100
Source data is obtained from IQVIA National Disease and Therapeutic Index.

Table 3: Proportion of fluoroquinolone treatment visits over all treatment visits among surgeons.

	2014 (95% CI)	2015 (95% CI)	2016 (95% CI)	2017 (95% CI)	2018 (95% CI)	2019 (95% CI)	% change (2014-2019)
Urogenital							
All treatment visits	18544 (16567, 20491)	18379 (16449, 20309)	17548 (15706, 19390)	17559 (15715, 19403)	17216 (15408, 19024)	17256 (15444, 19068)	-6.9
FQ treatment visits	1181 (827, 1535)	1023 (716, 1330)	1089 (763, 1415)	977 (684, 1270)	1081 (757, 1405)	1251 (876, 1626)	5.9
Proportion use (%)	6.4	5.6	6.2	5.6	6.3	7.2	12.5
Respiratory							
All treatment	4641 (3849, 5433)	4447 (3688, 5206)	4527 (3754, 5299)	4423 (3668, 5178)	4326 (3588, 5064)	4311 (3576, 5046)	-7.1
FQ treatment visits	241 (131, 351)	278 (151, 405)	123 (41, 206)	142 (47, 237)	136 (45, 227)	97 (32,162)	-59.5
Proportion use (%)	5.2	6.2	2.7	3.2	3.2	2.3	-55.7
Gastrointestinal							
All treatment visits	7418 (6345, 8491)	6574 (5577, 7571)	7592 (6493, 8690)	6956 (5901, 8011)	6207 (5213, 7201)	7689 (6576, 8802)	3.6
FQ treatment visits	264 (144, 385)	299 (162, 436)	246 (134, 358)	274 (149, 399)	231 (125, 337)	282 (153, 411)	6.8
Proportion use (%)	3.6	4.5	3.2	3.9	3.7	3.7	2.8

FQ = Fluoroquinolone antibiotics

All counts are in thousands.

Proportion use = FQ treatment visits/All treatment visits *100

Source data is obtained from IQVIA National Disease and Therapeutic Index.

Table 4: Impact of 2016 FDA advisories on fluoroquinolone use

Trends in fluoroquinolone use	Treatment visits	p-value (95% CI)
Pre-alert period (2014 Q1 – 2016 Q1)	4780566	-
Pre-alert change per quarter	-9273	0.51 (-38184, 19637)
Post-alert period (2016 Q4 – 2019 Q4)	4094993	-
Immediate change (2016 Q4)	-641035	0.000 (-937368, -344702)
Before-after change in trend	-44539	0.036 (-85956, -3122.345)

Source data is obtained from IQVIA National Disease and Therapeutic Index.

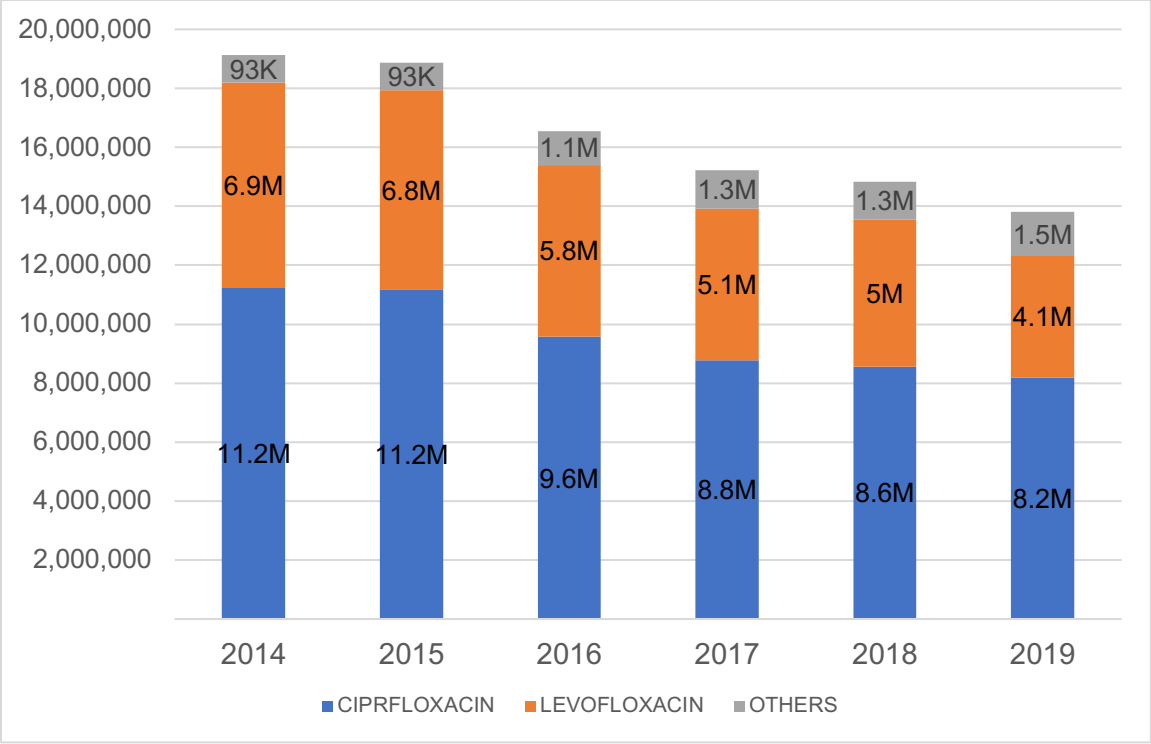


Figure 1: Annual utilization of fluoroquinolone antibiotics

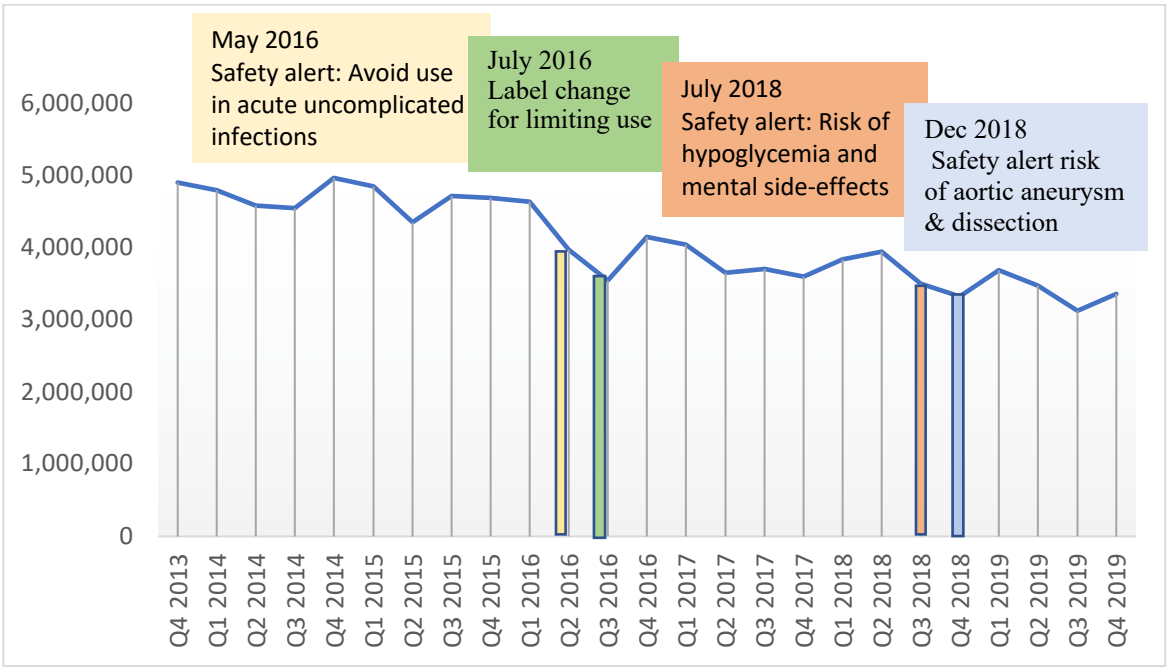


Figure 2: Per-quarter utilization of fluoroquinolone antibiotics

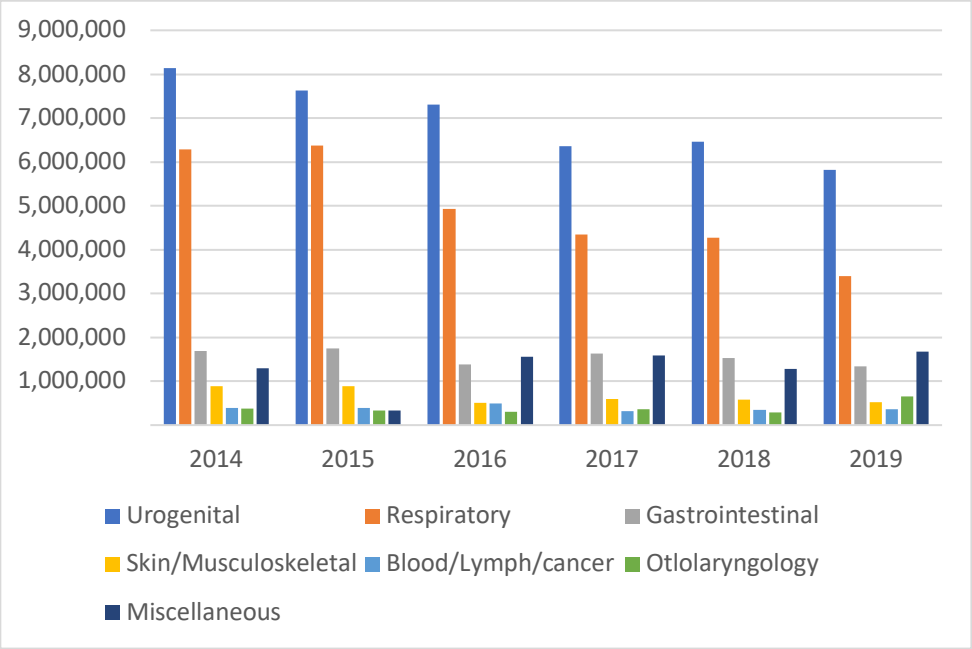


Figure 3: Annual utilization of fluoroquinolones by diagnoses

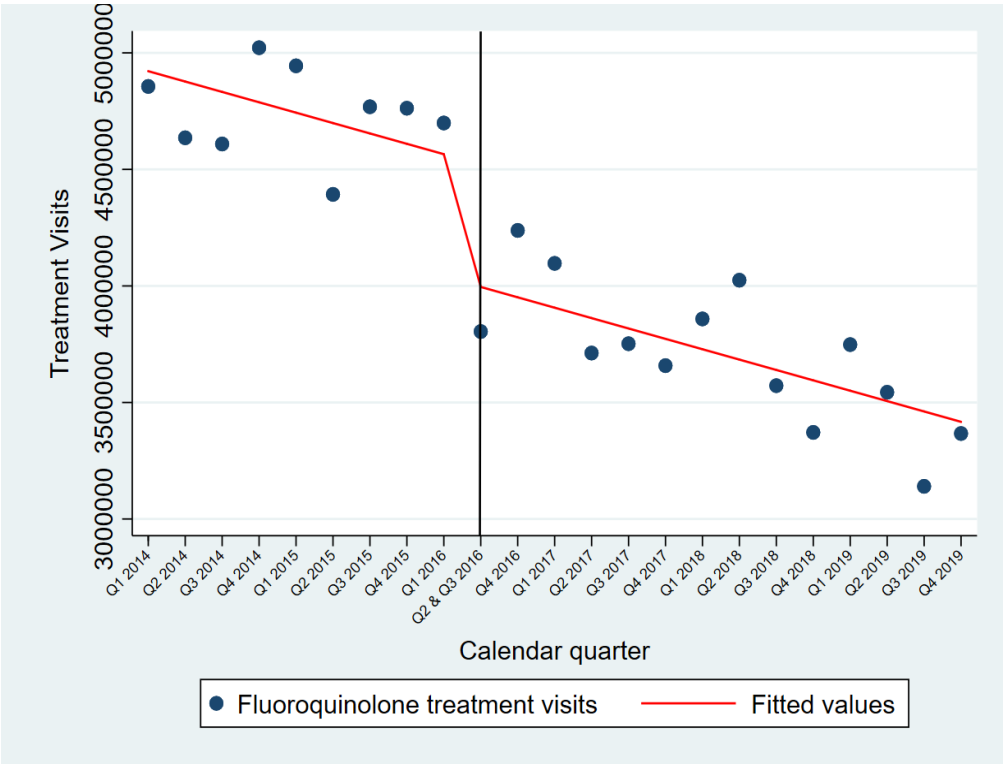


Figure 4: Impact of 2016 FDA advisories on fluoroquinolone use

APPENDIX

APPENDIX 1

U.S Food and Drug Administration Safety Communications for fluoroquinolone antibiotics, 2008-2018.

Date	Type of Alert	Description
July 2008	Black Box Warning	Increased risk of tendinitis and tendon rupture.
March 2011	Label change Dear Healthcare Provider Letter	Potential for myasthenia gravis exacerbation.
August 2013	Drug Safety Communication	Risk of peripheral neuropathy.
May 2016	Drug Safety Communication	Avoid use in uncomplicated acute sinusitis, acute exacerbations of chronic bronchitis and uncomplicated urinary tract infections.
July 2016	Label Change	Strengthening of 2008 boxed warning. Addition of information on risk of peripheral neuropathy and mental disturbances in boxed warming. Class-wide change in drug label: Indication of use modified as per May 2016 alert.
July 2018	Drug Safety Communication	Risk of serious hypoglycemia which can lead to coma. Risk of mental health side effects - disturbance in attention, nervousness, memory impairment and delirium.
Dec 2018	Drug Safety Communication	Systemic fluoroquinolones can double risk of aortic aneurysm and dissection.

APPENDIX 2

Categorization of prescribers as per the specialty of care provided.

Prescriber Category	Specialties
Medicine	Emergency Medicine, Family Practitioner, General Practitioner, Geriatrics, Internal Medicine, Osteopathic, Neurology, Dermatology, Podiatry, Psychiatry, and Internal Medicine Subspecialties (Allergy, Cardiology, Endocrinology, Gastroenterology, Hematology, Nephrology, Oncology, Pulmonary, Rheumatology)
Surgery	Colon and Rectal Surgery, General Surgery, Orthopedic Surgery, Ophthalmology, Otolaryngology, Obstetrics & Gynecology, Urology

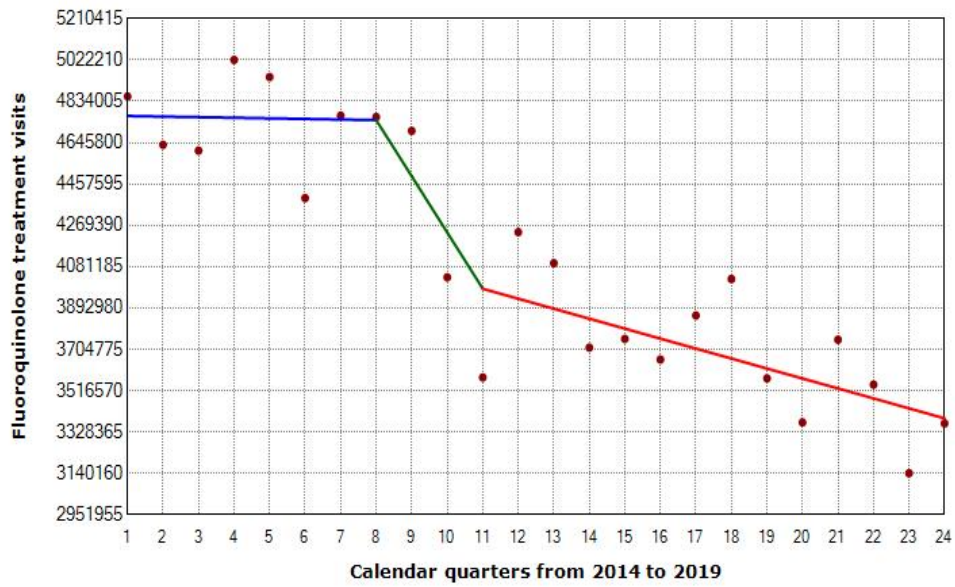
APPENDIX 3

2017 NDTI 95%, 90% and 80% precision estimates

Projected Count	Confidence Intervals		
(000)	**95 %**	**90%**	**80%**
2,000,000	2.09	1.76	1.37
1,000,000	2.67	2.24	1.75
900,000	2.77	2.32	1.81
800,000	2.89	2.42	1.89
700,000	3.02	2.54	1.98
600,000	3.19	2.68	2.09
500,000	3.40	2.86	2.22
400,000	3.68	3.09	2.41
300,000	4.07	3.41	2.66
200,000	4.69	3.94	3.07
100,000	5.98	5.02	3.91
90,000	6.20	5.21	4.06
80,000	6.46	5.42	4.23
70,000	6.77	5.68	4.43
60,000	7.15	6.00	4.67
50,000	7.62	6.39	4.98
40,000	8.24	6.91	5.39
30,000	9.11	7.65	5.96
20,000	10.50	8.81	6.87
10,000	13.39	11.23	8.75
9,000	13.89	11.66	9.08
8,000	14.47	12.15	9.46
7,000	15.17	12.73	9.92
6,000	16.01	13.43	10.47
5,000	17.06	14.32	11.16
4,000	18.45	15.48	12.06
3,000	20.40	17.12	13.34
2,000	23.52	19.74	15.38
1,000	29.97	25.16	19.60
900	31.10	26.10	20.34
800	32.41	27.20	21.19
700	33.96	28.50	22.21
600	35.84	30.08	23.44
500	38.21	32.07	24.98
400	41.31	34.67	27.02
300	45.69	38.35	29.88
200	52.66	44.20	34.44
100	67.12	56.34	43.89

APPENDIX 4

Joinpoint regression analysis for quarterly use of fluoroquinolone antibiotics, 2014 to 2019.



For X-axis:
1 - 4 ≙ 2014 Q1 to 2014 Q4
5 - 8 ≙ 2015 Q1 to 2015 Q4
9 - 12 ≙ 2016 Q1 to 2016 Q4
13 - 16 ≙ 2017 Q1 to 2017 Q4
17 - 20 ≙ 2018 Q1 to 2018 Q4
21 - 24 ≙ 2019 Q1 to 2019 Q4
*Indicates that the slope is significantly different from zero at the alpha=0.05 level
*The dotted points show calendar quarters
*The solid line is fitted joinpoint time series.

DISCLOSURES

Dr. Alexander is past Chair of FDA's Peripheral and Central Nervous System Advisory Committee; has served as a paid advisor to IQVIA; is a co-founding Principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a member of OptumRx's National P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. Dr. Cohen is a paid consultant to Monument Analytics. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies.

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BIOGRAPHICAL STATEMENT

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Overview

Siddhi Umarje is a graduate student at the Johns Hopkins Bloomberg School of Public Health. Siddhi received her Pharm.D. and completed clinical pharmacy residency at Bharati Hospital and Research Center in 2018.She has two years of clinical experience and one year of research experience in India. She is pursuing formal research training in epidemiology, focusing on clinical & cardiovascular epidemiology research, and pharmacoepidemiology research. She is a Center Scholar at the Center for Drug Safety and Effectiveness and a part-time Research Assistant in the Department of Epidemiology at Johns Hopkins School of Public Health. In 2019, she worked as a pre-doctoral research fellow at the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham & Women's Hospital and Harvard Medical School, Boston. Her research interests include drug safety, comparative effectiveness, drug utilization, and pharmacovigilance.